JOHN KIRBY: So, professor, if you could just begin by telling us your name and a little bit about your background?
DR. IOANNIDIS: I'm John Ioanniddis. I'm a professor of medicine and of epidemiology and population health at Stanford University. I'm one of the two directors, co-directors, of the Meta-research Innovation Center at Stanford or METRICS. My research is interested in appraising evidence, in trying to understand data, strengths of data and weaknesses of data, and trying to make sure that we have the most useful information to make decisions that matter.

JK: You recently wrote an article that caused a lot of discussion. Can you tell us why you wrote it?

DI: So, this article was trying to appraise the current situation regarding COVID-19. COVID-19 is clearly the major challenge that we are facing as a country, as the whole world, actually. It is a major threat. We need to act with alacrity, and we need to act having the best data. We need to act having reliable data. Unfortunately, much of the information that we have collected so far, and this is not to blame anyone, it's just something that has arisen very fast and has caught us off guard, in a way, it's a new pandemic, most of that information is not reliable. We have increasing evidence that many of the key features that pertain to what this pandemic is about, how lethal is that virus, how many people it has infected or will infect, what is likely to be the eventual impact, and how effective are the different measures that we are applying - we have major gaps in practically all of those fronts. So, it is imperative that we try to cover this lack of unbiased evidence as quickly as possible.

Of course, we need to act immediately. We cannot wait for perfection. But at the same time, as we make decisions and as we act, it is important that we couple that with immediate collection of the most reliable information to inform us about where we are, where we are heading, and whether our measures have made a difference for the better or for the worse.

JK: What was your concern in writing the piece? It seems there's a major concern even embedded in the title?

DI: So, COVID-19 has been called "The Pandemic of the Century." It's a once-in-a-century pandemic, and clearly in terms of what we see and what we hear, and the mobilization and all the news and all the deaths that we witness, clearly it is a major threat, or I would say, a threat with unknown potential, in terms of its eventual impact. At the same time, I call this as possibly being a once-in-a- century evidence fiasco. Because we are dealing with such an unknown and uncharacterized evolving threat with very limited data. Many of our actions are just based on gut feelings, trying to do the most, trying to do our best, but without knowing whether some of them will lead to more harm than good. Unless we do get reliable information, we may just continue doing whatever we do with the best intentions but doing it just blindly.

JK: What can we actually say about the rate of contagion and the lethality of COVID-19 at this point? Is it as bad as the WHO originally said, 3.4% death rate? Can we say that with any firmness? Are we sure the death rate is worse than that of the seasonal flu, etc.? Can you just talk about what we can actually know about it?

DI: So, this is a major debate, and data are evolving on an hourly basis. So, I will tell you what we know as of now, but it may change very quickly. The WHO indeed released an estimate of a case fatality rate of 3.4%, which, at the time of the release, earlier in March, it was based on the number of people who had died as the nominator, and the number of people who had documented infections as the denominator. This is a crude estimate, and it largely depends on our ability to capture infections that are in the denominator. The number of deaths, hopefully, is captured with more accuracy, even though, even for that number, there can be some debate. For example, whether these

deaths are by SARS-CoV-2 or with SARS-CoV-2, or also whether some deaths are missed, or whether some people who are infected now may die later, and we have not captured these deaths yet. But the bigger uncertainty is about the denominator, because based on what we know now, many people who are infected with this coronavirus, they present with very little - either no symptoms or mild moderate symptoms that are very difficult to distinguish from the common cold and common flu. And many of them, apparently, would not present for asking for health care and for being tested.
So, what we know is just the tip of the iceberg. And information from settings where we have more complete information about that denominator suggest that the infection fatality rate is much, much lower than 3.4% it is actually probably much lower compared to the .9% that is the main figure that went into some influential calculations by a wonderful team of researchers at Imperial College which
probably overestimated the exact infection fatality risk.

JK: What about something like Swine flu from years ago now, in 2009, 2010. So, according to the CDC, it globally infected 1.4 billion people and killed between 151,700 and 575,400, and they had 60 million cases in the United States, 274,000 hospitalizations, and 12,500 deaths. And while they were frighting stories in the media at the time, there wasn't nearly this level of response. So, what makes this different?

DI: I think that each virus, each new virus is a different story. And it is justifiable to respond with alacrity and to not consider that this will be just yet another season with another situation like the swine flu or like what happened in 2009. In the past, most of these claims for major epidemics that would be devastating eventually, the projections and the predictions that were made early on were not validated, so the early estimates suggested that this would have a tremendous amount of mortality and cumulative number of deaths would be amazing. Eventually, the number of deaths were far more modest than the original projections.
This doesn't mean that with the new Coronavirus we will see the same story again. It could be that, if not this one, maybe some other new pathogen in the future will reach that prediction of really exceeding by far what we commonly see every season with influenza. This makes for an argument that we need to be better prepared to get the most reliable information possible because not only this year’s outcomes are at stake, but also any other future situation where we may be meeting uncertainty. So, it's very important that we get it right. It's very important for lives being at stake, it's very important for public health, for science, for really making sure that we have as accurate estimates as possible.

JK: What would that entail? If you could just describe the testing protocol that would be necessary to get more accurate numbers?

DI: Ideally, you want to have a situation where everybody is being tested to see how many people are really infected, rather than just wait to see what is the number of people who come to your attention. Obviously, this may be difficult, especially in a situation where you have a bottleneck in the production of diagnostic tests, although that bottleneck is hopefully gradually relieved as we speak. Aggressive testing is important but equally important, and probably even more important, is to have a random sample, a representative random sample, of a population that can tell us by extrapolation what is the number of infected people in the general population. We do have some situations currently where we are approximating that number with some fair accuracy.
One situation was actually a very early experience in the course of the pandemic. We have a cruise ship, Diamond Princess, where we had an outbreak of SARS-CoV-2. Many people got infected. This is a situation where you have a closed space, people cannot really go anywhere, they live in very close quarters together for the duration of the cruise, so we had an infection rate of close to 20%, 19% of the passengers and crew got infected, and among those who were infected, as of now,

1% has died. It is possible that some more people may die later on, not everyone has recovered yet, but this is a population where we pretty much know the outcomes of the infection on almost everyone who was on board. 1% is a figure that pertains to a population of mostly elderly people. The mean age of the passengers and crew was 58 years old, and the median, I believe, was closer to 65. And we know now that there is a very strong age gradient - people who are older have a higher risk, people who are young have a much lower risk. Children, especially young children, practically have zero or entirely negligible risk.
If you try to adjust for the age difference between the passengers and the crew and the general population of a country like the US, the age and gender adjusted infection fatality rate in the US population would be much, much lower than 1%. it may be .1, .2%. We need to have a lot of uncertainty around that estimate because only 7 deaths were recorded, so it's a very small sample size. And also, these people may not be the same as the general population in terms of what diseases they have, because we know that people who have severe diseases in their background have increased risk of serious outcomes, including mortality. But, allowing for these uncertainties, probably an estimate anywhere between 0.05 up to 1% may be more reasonable to consider, as opposed to, let's say, 3.4%.

There are a couple more settings where we have fairly unbiased data. One setting that has emerged in the last few days is data from Iceland. Iceland is a small country that really pays a lot of attention to science. They have a wonderful cohort. It's called deCode and they have set it up to measure genetic risk factors in the Icelandic population. They have decided to get volunteer samples to be tested and they do that for a number of days now. Obviously, it's not entirely random, but it comes as close to being random as possible, and until the last data that I saw, they had an infection rate in the population of .9%, which you extrapolate to 360,000 people in the Icelandic population. It turns out to be about 3,500 people being infected, and of those, only 1 fatality has occurred so far. We have 1 death, and there's also some people who have some severe symptoms. One death corresponds to 0.03% infection fatality rate. Obviously, if there are more deaths, that will go up. But if you compare that to seasonal influenza, which is 0.10%, it doesn't look that bad. It could actually be even less, compared to seasonal influenza, although I would not be surprised if it's higher but not really much higher.

The last situation where we have an entire city being tested is the city of Vò, in Italy, in a situation where we have the most dramatic events happening so far for the pandemic. That city had an early death of an elderly individual with underlying diseases, and they decided to test everyone in the population, so they tested 3,300 people, every single citizen, and they found an infection rate of about 3%. That was in the third week in February, so most likely, in other communities in Italy where the ability to contain the virus was not very successful, it's very likely that the proportion of people infected continued to increase pretty rapidly. It would not be surprising if in some locations in Lombardy, we have currently reached infection rates of 20 or even 30%, but this is still a bit speculative. If that's the case, then you need to correct the infection fatality rate or case fatality rate for Italy that seems to be very high by a very large factor. it could be a correction of 100, for example, that needs to be applied and then the infection fatality rates would drop again close to the range of seasonal influenza.

JK: Given the preference for randomized general samples, what do you think of the recent decisions in New York and California to only test those who are sick and in hospital? What sort of data will that give you? Is it useful data?

DI: So, these data are important to get for medical care, for really trying to make the best decisions about single patients, and we need that information to be available for example for some people with chronic diseases and who are debilitated - it makes a difference to know if they are infected or not. It may affect their management, even if they do not have symptoms, and also, if you have

someone who presents with severe symptoms, it is important to know whether or not they have been infected by SARS-CoV-2 or not, so as to be able to make the best decisions. Of course, we don't have established treatments that we know for certain that they work, but there is many potential treatments out there and there is the possibility for these people to be enrolled in clinical trials or try some empirical therapy to see if they might do better in that regard. So, it's not wrong to do it for these single patients, one at a time, but this information is just giving us the same type of data that we have so far from many other countries in terms of the epidemiology, which is so unreliable for getting the big picture, as I described before.

JK: And so, if it's possible that the death rate in Italy would need to be corrected by a factor of 100, what explains - I mean, we hear that there and in so many other places, that the medical system is already being overwhelmed, and there are these shortages, so what would account for that, if indeed the death rate is likely lower than they say it is?

DI: I am collaborating with scientists who are leading the Italian response, and I'm trying to get their insights. This has been a very interesting puzzle that we have been brainstorming on. There are multiple explanations so far that can be proposed on why Italy really became such a disaster. And these include the following: first of all, its demographics. Italy has the most elderly population in Europe, and one of the most elderly populations in the world. It is far more older people on average, compared to a country like the US or most of the other countries, and we know very well that SARS-CoV-2 has a markedly steep increase in mortality in people who are very old. The average age of people who die in Italy is 81 years old, and also, most of these people have lots of other underlying diseases. Italy is a country that has a very strong history of smoking, it has very high rates, therefore, of chronic obstructive pulmonary disease, it has very high rates of coronary heart disease and these are very strong risk factors for having a bad outcome in this infection. If you wanted to transplant this data to another population, you need to account for that differential case mix and try to adjust accordingly what your expectation would be in a different country.

Another observation that has emerged is that many of these people probably would have had very limited life expectancy in the absence of that infection, and it still remains to be decided how many of these infections are deaths with SARS-CoV-2, versus deaths by SARS- CoV-2, meaning that the virus has the key influence on the outcome, rather than just giving a final kick or participating among many other factors in shaping the outcome, but these people are having multiple other reason that they would have a very poor endpoint and eventually die, many of them. There's also other things that probably got wrong in Italy. Italy has a relatively low number of ICU beds per population. It has about a third of ICU beds per population compared to the US. And their system is running at full capacity practically every winter, at 95-98%, so if you get just a little bit extra, you're very close to the point of collapse. And we know that in winter, there is a 25-30% increase in the number of deaths compared to summer months. A major part of that contribution is deaths due to respiratory pathogens and typically, every year, this is due to influenza. Now, this year it could be influenza plus SARS-CoV-2 but you realize that a system that is so close to saturation, to having its maximal capacity, if you add just a little bit more, It can very easily collapse.
Italians were the first to be hit in Europe, and that was an exotic pathogen. Everybody thought that they had to do their best, so they said, "we need to admit these people to the hospital," even if they had modest or not-so-severe symptoms. This resulted in a very bad decision making, and I think that this is something that every other setting that is hit by an epidemic wave needs to avoid. By admitting these mild or moderate cases, very quickly they became saturated, and when they started getting the severe cases, they just had no room for them. Also, the hospital became heavily colonized with that new virus - this is a virus that can stay on surfaces - many of their medical personnel got infected in the heavily infested environment; about 3,000 people in the medical personnel in Italy got infected, and they had to leave the battle to be in quarantine, making things even worse. So, there is a lot of factors that created like the perfect storm.

If you add to that some probably lack of some strict measures in the early phases, for example, lack of strict personal hygiene might have been an issue; large congregations - in one setting in Bergama, which is the city that has been most hit by this pandemic to date, there was a match of champion league that attracted wide attention and about a third of the population of Bergama not only saw the match, but they also celebrated until very late hours after midnight embracing and dancing and probably kissing each other, who knows, and you had tens of thousands of people out in the street in very, very close contact. There's lots of things, I think, that explain much of what we see in Italy. We also need to consider that it is an outlier. We have 200 countries, and they have the worst outcomes today, and even within Italy, it's not the entire country, it's specific cities and specific hospitals, actually a small minority of hospitals, that faced these extreme odds. And so, pretty much, a situation of crashing because of the load of cases.

JK: Going back to this idea of the dangers inherent in an overreaction, is your sense now that social distancing is the appropriate response? And for how long a period and at what point, given what we are starting to understand about some of the problems with the data, how long should this go on and until, and at what point does it become, as you're suggesting in the piece, worse than the actual illness?

DI: What we know is evolving very fast, and it seems that social distancing, as well as aggressive tracking of cases and contacts and self-isolation did work very well in cases like Taiwan and South Korea where everything was coupled with very aggressive diagnostic testing. People really went out to try to make sure that they did find every case and every contact. Of course, they missed a lot I'm sure, but they captured far more compared to, for example, what has happened in our country. That seemed to work, and of course, this is as of now, because we don't know if there will be a resurgence of a new epidemic wave. In situations where you have, probably, a very large number of cases in the community, many of them asymptomatic or undetected, we just don't know what is the best strategy. I believe that the measures that are taken should be taken because we need to do something. At the same time, though, we need to get an estimate of where we stand, how many people are infected, and how does that change, because we need to make decisions within a week, within two weeks, three weeks maximum, that are informed by reliable data.

If we shut everyone in their house, it is a solution. If we manage to even isolate everyone, not even being in touch with any other person, in theory, we are containing the spread of the virus. As you realize, this is very difficult to do. It has lots of consequences, and for a society like ours, it means that very soon you will start seeing a major impact on the economy. We already see that. If the economy is ruined, you have unemployment, you have poverty, you have bankruptcies, you have lots of diseases that are associated with this sort of social and economic disruption. We have strong evidence that that can lead to an increase in depression, in anxiety, in suicides, in heart attacks - in common things, in things that cumulatively could have a much higher impact on deaths compared to what SARS-CoV-2 can achieve on its own. So, there are some models that suggest that if you go down that path of basically lockdown, you may need to wait for 18 months.

And I'm extremely worried about that scenario. I'm not sure that our world, our civilization could survive that. I think there are not just millions of lives that are at stake, which is the pessimistic scenarios about SARS-CoV-2, it is billions of lives who might be at stake if we have to protract that for so long and my plea is to get the best data. Because we have very serious decisions to make, we should make them as informed as possible. I'm perfectly happy to be in a situation of practically lockdown in California, more or less, shelter in place
but I think very soon we need to have that information to see what we did with that and where do we go next.

JK: So, we hear a lot about the shortage of respirators and the shortage of masks and apparently at Columbia Presbyterian, they went from 4,000 masks a day to 40,000 masks. Does that make sense statistically to you, that that would be happening at this moment, that this overwhelming burden would emerge so quickly in New York, for instance?

DI: The worst advice here would be panic, because we have seen, for example, as far as masks are concerned, that very early there was the feeling that every citizen should just stock in masks and other protective gear, and that resulted to a shortage of having that available for hospitals where they are really needed. So, this is a situation where lack of evidence is one nice example, is leading down the wrong path, is leading to the wrong response, it is depriving this protective gear from the places where they are badly needed. I think that we should expect substantial differences on how different hospitals are affected. It's very likely that the large majority of hospitals will not be affected. Even [in] Italy, that is the horrible disaster that we were talking about, the vast majority of hospitals did not have a problem. But some hospitals did have a major problem.

What can we do? We can plan ahead. We can plan to have extra resources, and actually we have to do that acutely in this case, because we don't have too much time. We can think about having mobile resources that could be allocated to hospitals that are at high need, because we just don't know exactly where we might need that extra surplus, so if we say that we allocate something to a specific hospital, it could be that that hospital never gets anything close to what we are imagining, while some other hospital might get that. We also need to prepare based on what we expect, given the demographics of the catchment area of each hospital. If you have a hospital that is covering a huge population, mostly of elderly people, and people with severe background diseases, that is a very different story compared to a hospital that has a very different case mix in the background population that it serves. We need to think smart, and I want to remain optimistic that if we do not panic, things will be okay. I don't want to diminish the size of the problem and of course there is uncertainty and people may have that fear because of that uncertainty, but there is a very good chance that we will be able to weather the storm.

JK: You mention in your article other so-called mild coronaviruses, some of which can have fatality rates, you said, as high as 8% among elderly people in nursing homes. Can you just speak generally about the coronavirus as an entity, or as multiple entities, and are we absolutely sure and have you, personally, seen the epidemiological data to show that this is indeed a novel coronavirus?

DI: So, there's no doubt that this is a novel coronavirus. There have been coronaviruses that do cause a large number of infections in the community and in different settings, practically every year. There are two coronaviruses that are very lethal - those that caused SARS AND MERS, and these, fortunately, were very rapidly contained, so the number of people who died was relatively very small, compared to what we see in a typical season, just by influenza. The four common coronaviruses occur more or less every year. Some years, you may have more of one or the other, and they infect, probably, a very substantial proportion of the population. They also cause, probably, substantial deaths, or, at least, we don't know exactly what their exact positive contribution is, but they are seen in people who are hospitalized and people who have severe conditions and perhaps they contribute eventually to that mortality. We don't really track them that carefully, because nobody has paid attention to them, even though they're known for decades, we just take it for granted that they are out there. They contribute to that larger bin of what we call, "influenza-like illness," and even for influenza, we do not try to make a diagnosis with laboratory testing in every single case. We test about a million people in this country every year for influenza. About 200,000 of these samples are positive, and eventually, we estimate that we may have 30-60 million people infected with influenza and probably 25-60,000 or more deaths per year every winter like this winter from influenza in the US, and similarly in other countries.

Within that bin of deaths of influenza-like illness, it's very likely that you have other viruses and corona viruses are part of that mix. We haven't paid attention. You know, we just felt that it's not going to make a difference, we would not be treating these people with any drugs, we would not be doing anything different if they have severe disease, we would admit them and try to oxygenate them. We would try to support their respiration and their vital functions and see whether we can save them in that way. So, this is a new coronavirus that has created far more anxiety because we have seen these dramatic presentations early on in the course of the pandemic and we are struggling to understand how much different it is in its potential to kill people to cause severe damage compared to what has been going on every year.

This is where the big debate is, and unless we get the denominator of how many people they are infecting, it will be very difficult to get a reliable answer. What we know is that even these mild coronaviruses, if one could call the mild, that circulate every year, when they hit elderly and debilitated people, they can be devastating .So, there have been descriptions of outbreaks in nursing homes where elderly were infected and they carried the case fatality rate of 8-11%, so very high, even though the majority of people who were infected in the community probably would not even notice - would just feel that they have a common cold or something very minor.

JK: So, if we hadn't made a production of this, and you seem to indicate this in your article, to some degree, is it possible if we weren't really looking right now, this could just be a bump or not in the general package of, or bin as you call it, of influenza-deaths? Is that, at the lower end of the scale, or even the middle range, is that not a possibility for this virus?

DI: It is a possibility. As I said, we still have a lot of uncertainty on what would be the exact evolution of this epidemic. We still see that there's growth in the number of cases and in the number of deaths, but let's say that - and this is an entirely hypothetical scenario - that that new coronavirus was not detected, no one had noticed it, and no one had found that this is a new entity, and eventually it killed 10,000 people in the US based on this presentation that you have respiratory distress syndrome, acute respiratory distress syndrome. Most likely, you would have counted that within the bin of influenza-like illness which, as I said, is killing already 30-60,000 people. 10,000 more or less would be very difficult to peg, it would be well within the range of statistical noise. And probably no one would have noticed or perhaps some experts would have said that this year influenza seems to have higher activity, and maybe give some advice to increase the vaccination rate. If it were 10,000 deaths, it's very likely that it would not have been noticed, people would not have paid attention, if there were some news story, as I say in my article, it would have attracted less attention than a game between two indifferent NBA teams.

Now, this doesn't mean that that's going to be the final outcome of this pandemic. There's a chance that we may end up with far worse outcomes or there is even a chance that we may end up with even less compared to 10,000 deaths in this country. This is why we need data. We need, urgently, data to be able to get some sense of where we are and where we are heading.

JK: Is there a major difference in the way this illness presents itself? And have you spoken directly to doctors on the ground who have treated patients with confirmed cases?

DI: I think that the clinicians have now seen a number of cases, in some places more than others, and I think it is very useful to have the information about the clinical presentation of this new infection. In mild and moderate cases, it is very difficult to distinguish the symptoms compared to what is the common flu, or even the common cold in some mild presentations. In severe cases, we have presentations that fit what we call the severe respiratory distress syndrome and this is really grave. This is a very serious condition, and of course in several cases, it can be lethal. I would be very careful to make inferences based on single case reports and anecdotes. I feel that every single

patient has the dignity of his life and every single patient is a different story. and we have to give great respect to that life and that person, but I am worried that if we see, in the news, presentations of single cases as heralded as being "something that I have never seen before," "this is so horrible," "that's the worst case of severe respiratory distress syndrome that I have seen," we are falling into a trap of sensationalism, we are trying to make sensational comments about every single death that is happening.

And severe respiratory distress syndrome is a major problem. It does kill people, and it kills people regardless of the exact ideology, the exact reason, the exact virus or pathogen that is responsible. I think that we should try not to panic. We should do our best we should try to protect, also, our medical personnel. We don't want them to be infected, we don't want them to of course, get sick from that, and we also want them to be available for fighting that battle but just describing single cases, one at a time, with screams of horror is not something that helps

JK: And, doctor, to that point, you were saying that if this had not been singled out in some way and given that most of these symptoms present exactly the same way as a flu or a cold, it might have gone unnoticed. How does that square though with what seems to be this major stress on, say, the New York healthcare system? If this was just, let's just say it was another flu, would we still be seeing the same sorts of stress? or are you saying that the panic helped engender the stress?

DI: I think it's a combination of both and even with influenza, we have variability in the rates of infection in different localities and in different hospitals that get more of an infectious load every winter. And as I described in the situation of what happened in Italy, it was some hospitals that were completely overwhelmed, and most others were not. So, there is that variability and we need to take that into account. But, it's not just the average variability that we see every year. You have on top of that a very acute situation, a situation of perceived crisis, a situation of crisis. You have media following every step and every second what is going on with every patient, with every single death. I mean, can you imagine what would happen if the sixty million deaths that happen every year on this planet we had a meter counting them, one by one, and having stories written for each one of them? It would be horrible. I mean, we have gone into a complete panic state measuring so far, a sizable number of deaths but nothing close to the total cumulative mortality that we see both in this country and around this world. I think that panic component and that over-emphasis of media attention is probably making things worse. We do want to sensitize people to follow instructions, to try to keep the public health measures, to shelter in place, if they have sheltered in place, but we don't want to get them scared. We don't want them to get into panic. This doesn't really help.

JK: Now, if it ends up having a similar mortality rate to the seasonal flu, would this tend to portent a whole new normal, in terms of our reaction to respiratory distress syndromes? Should we be doing social distancing for the regular flu or for other forms of corona? I mean, people are talking about telemedicine, distance learning, they are talking about a whole new normal in social interactions as a result of this. Is this the appropriate response to what we are seeing?

DI: I think that we need to be patient and not panic and not reach forgone conclusions at this stage. There is a lot that we have to learn, and I think that there is a very high chance that we are exaggerating. As we discussed, many of the features of this pandemic, of course, are serious, but I think that the estimates are exaggerated. And I think that they are at risk of really making some fundamental decisions about the structure of our civilization, of our society, of our future that may not be appropriate. I think that we have no clue how a society would work if you need to build it around a construct where everything is done from a distance. I'm willing to accept that in a short-term you want to do your best and throw your best tools and try everything, but thinking of a society that is just entirely imprisoned and telecommunicating is a very different beast and it's something that, I am not even sure if it is tenable, it creates a very different environment, it creates a

different environment for our ethics, for our ability to socialize, for our democracy, for what it means to be human, for what it means about our perception of risk and our perception of how to deal with risk. I think it's very early to doom our world in a future that seems really horrible.

JK: You have been famous for identifying that somewhere upwards of 90% of medical studies, drug studies, have major flaws and are essentially wrong. Are you concerned that in this kind of climate they'll be a rush to prescribe both therapeutic drugs, a rush to develop vaccines, that may in fact not do what they say or be in fact worse, also worse, than the cure?

DI: Let me qualify that statement: I haven't really claimed that 90% of scientific papers are wrong, but, a very large proportion. On average, probably the majority do have problems and they could be false when they are claiming major discoveries of new things that have been found. Science is the best thing that has happened to humans, but we need to do our best. It's very difficult to do science, you need full commitment, you need accurate data, you're struggling against error and mistakes, and I feel that myself. I am a champion of errors and mistakes. i just hope that I will realize them sooner rather than later and try to correct them. In a crisis environment, there is a push for making discoveries even faster. And we know from other fields that when you have that time pressure, when you have that anxiety, when you have that incentive to arrive at something that is extraordinary, there is a higher chance of getting it wrong. There is a chance that more corners will be cut; there is a chance that some standards will be removed that are safeguards to get reliable and useful results. For example, there was discussion about cutting some of the phases that are necessary for developing a new vaccine, like moving directly to humans without any safety information, and I think that's a horrible idea, I mean, especially for corona viruses, we know that the efforts had been made in the past to develop vaccines, and they didn't go very far. In one of them, 30 years ago, a vaccine was developed for a model of feline corona virus - you know, corona virus in cats - and it had worse outcomes in the group that got the vaccine, compared to the group that didn't get the vaccine, because the vaccine lead to some hypersensitivity. So, when the cats were infected with coronavirus, they did worse compared to not have received the vaccine.

Vaccines are the best discoveries that we've made in medicine. They're amazing. They have saved millions and millions of lives. We need to get it right and make sure that we get reliable evidence for good vaccines, for good treatments, for good interventions. I would argue, we need to test interventions on how we deal with patients in situations of crisis. We need to test interventions on how we apply social-distancing measures in the most effective way. All of these are interesting questions to address with science. Not with panic, not just with gut reactions. Gut reaction is okay for the immediate response, but immediately after the immediate response, you need reliable science, you need objective calm accurate appraisal of the evidence.

JK: Do you think it's appropriate that the various governors are 23 talking about setting up hospital beds in parking lots in Nashville or a gym at Yale or the Javits center in New York? Is that warranted at this point?

DI: I think that preparedness is a good thing because we just don't know exactly what the epidemic peak will look like and how high it will go given our efforts to flatten the curve. So, I will not blame anyone who is asking for preparedness and is asking for resources to be in place to make sure that we do manage to win that battle. At the same time, that preparedness and the extremes should not be taken as best estimates of expectations. What I would say is, prepare for the worst, but base your estimate, your best guess, on the average of what you think might happen.

JK: Do you think that there is something to the idea that this is a political problem somehow caused by the policies of the Trump administration? Is it true that Trump abandoned the concerns of

previous administrations is there anything to this idea that his early treatment of this has made things in some way worse?

DI: I'm just a poor scientist, I'm not a politician, and I do not want to become one. i think under these dire circumstances it is important that we remain as united as possible that we try to not end up quarreling with each other and of course, try to learn and make justified criticism about what the shortcomings have been in, for example, public health or our ability to prepare for crisis. We need to learn. I think that there is a risk that in this situation, there may be other conflicts and other interests that get interspersed and they kind of take over the entire agenda. That should not become a political debate, that should not become a debate between people who may have different financial conflicts or other conflicts. It should be something that we should all be united about, saving lives, getting the best outcome, and really knowing what are the next steps about, what we do with this epidemic, and what we do with our world at large.

JK: Apart from the deaths of despair that can result from sheltering in place and being without a job or outside of school, do you agree with the doctor, Dr. Katz, who wrote in the New York Times that sending kids back home to be with their perhaps more elderly or more immune compromised parents may be adult children who are in the workforce who have to leave where they are and go back home, could that potentially, just on a medical level, on a contagion level, create a problem?

DI: I think that David Katz raises a valid concern. Since we do not know the level of infection rates in the population at the moment, especially in a population like young children, but also even adults, we really don't know what is the proportion of infected people who we are locking in along with their elderly parents and relatives and frail relatives who suffer from chronic diseases. And what we know, based on theory and some empirical observations, is that when you have a lockdown, or a shelter in place, you hope to diminish that very rapid dissemination of the virus in the wider community. But you run the risk, at the same time, of a lower scale but still pretty substantial dissemination of the virus within these closed spaces that we ask people to stay [in]. So, if you get these children in their houses at a point in the epidemic curve where many of them are infected, it may not be a good idea. If you do it at a situation where very few of them are infected, then yes, you are gaining some time, but even then, you don't know whether that time is just short-lived. And once you remove these measures, you are back to square zero.

I mean, you have probably protracted the problem to appear a bit, but it comes back with a vengeance once you relieve the measures. We have to have data to be able to tell what is the optimal intervention? What is the best timing? What are the best components of these interventions? There are different components: what to do with schools; what to do with social distancing; what to do with protecting elderly with isolation; how severely you try to implement these different measures; how do you facilitate different possibilities to make sure that these measures are adopted? It's not just throwing everything [at it] and hoping that it will work - this would be medieval medicine, and I'm scared to believe that in the 21st century we just go blind and throw medieval medicine in the entire population of the entire world.

JK: I mean, I know I'd just be asking you to guess, but wouldn't it make more sense as some have suggested to isolate the vulnerable portion of the population and let the economic and other life of the country and the world continue taking other appropriate measures? Doesn't that, on the face of it make more sense for something that seems to be about as dangerous as this is? Even within the full range?

DI: Depending on what is the stage of the epidemic and how many people are infected, it may be that a solution of, indeed, isolating those who are at high risk and making sure that we protect them as fiercely as we can while letting the rest of the society continue their work and try to maintain the economy and also support these much fewer numbers of individuals who are at risk - it may make a

lot of sense. And I think we need data to decide if this is the best course, versus a blind lockdown that would last forever with very uncertain outcomes. But we need data. It may be the best idea, and I'm thinking myself that it may be an excellent idea, but I'm completely open to be refuted, because we don't have the data at the moment to validate it. Once we do, I think we should act as quickly as possible.

JK: You've made an incredible splash over the years just looking at bias in studies and looking at bias in the way in which scientists go about their work and they've actually thanked you for it. They haven't felt hostility towards you. What if you were to give an assessment of what biases may have been at work in pushing us towards this particular solution of general lockdown, what might your assessment be?

DI: I think that it's still early in the course of the epidemic to make definitive conclusions about which biases were more influential. I think it would be very important, once the dust has settled, to try to dissect what went wrong and what was the appropriate response and try to learn from that. I believe that there is a domino effect. I think that once you believe in some exaggerated estimates, and you start making decisions that may be extreme, there's a sense that if you don't follow up with even more stringent decisions and even more severe decisions, you may be claimed to be negligent, and there is a risk that even leaders who have lots of faith in their judgement, if they see that other leaders are following a specific path that is very aggressive or conversely, is not aggressive at all, they may feel that they need to follow suit and have that domino effect.

So, there's bandwagon effect, there's domino effect, and in the meanwhile, most of that is happening with no evidence. There's also a lot of that media halo that is surrounding this whole adventure. If you just go to Google - I did that, and I just typed "coronavirus," and you get something like nine billion results. If you type influenza, you get something like a hundred million results. So, I think that we have really a pandemic of news stories and news clips and anecdotes about coronavirus. And I don't want to diminish its importance, but we need to get solid evidence along with the anecdotes, at a minimum.

JK: Didn't this sort of begin early on in January? Because on January 30th, 2020, the WHO declared a public health emergency of international concern. And that was when there were only 150 cases outside of China. I mean, did that decision make sense then, and in retrospect, does it make sense now? That they were so early to raise the alarm, with just 150 cases outside of China?

DI: I would definitely not blame the WHO. I think that 28 they are in a very difficult position. They are trying to make judgement calls based on information that is acute, that is evolving very rapidly, and that is pretty unreliable, as we have been discussing. So, they have to do something. And maybe they did the best that they could. It would be the wrong course in this situation to start accusing people for doing too little or too much. It would mean that some of us know everything, we know everything of what will happen with this virus and this epidemic, and this is clearly not the case. We do have uncertainty. So, I fully respect people who have different views and different estimates and different judgements compared to mine at this point. And there is no battle to prove that someone is right or wrong. I think that we need to get it right and it doesn't matter who exactly is more right than someone else.

JK: If it turns out that this is around the same sort of thing in terms of numbers and elsewhere and in severity as the seasonal flu, what do you think, what would the appropriate lesson to be taken be?

DI: I think this would be a major lesson. It would mean that next time, we would need to give a lot of emphasis in accruing these unreliable, unbiased data as quickly as possible, that we should think of mobilizing science as quickly as possible, which means probably means more aggressive testing,

more aggressive tracking of contacts, more aggressive testing of random samples of the population very early on. And of course, it would just add one more experience to our momentarium of dealing with epidemics. I really get a bit scared if this pandemic does not end up being as severe as it has been claimed in the beginning, where the expectations have been that perhaps 50 million people will die, if not more. It will be wonderful to show that this is not the case and far, far, far fewer people eventually succumb to this deadly disease. But then we really have to fight very hard to make sure that we do not lose the confidence of the public in terms of what it means to have science and to make proclamations based on science. Science is the best thing that humans have available. We should defend it and we should defend it's reputation. And not have people think that, "Oh, you know what? We've heard that before, this year it's just the same scam." That would be clearly the wrong reaction and the wrong message.

JK: Well, wouldn't governments defend their response simply by saying that the sheltering in place worked and that's why we didn't have the huge numbers that we've had? I mean, how would you refute that sort of a statement?

DI: Well, I think that we need to see what happens. And of course, sheltering in place did not happen early it happened pretty late in most locations. So, according to the theory that has been proposed, probably it wouldn't work that well. We need to see. Different countries had different policies. Not every country followed the same path. You have Taiwan and South Korea with very aggressive diagnostic testing, while keeping most of their society open; you have Iceland with even more aggressive diagnostic testing; you have Singapore, you have Japan, a different model. You have, even within Europe, a very different stance early on in the epidemic versus later decisions. You have the UK that followed a different path until recently, pretty much leaving everything open, schools open, even having large mass gatherings, more or less, until a few days ago going on.

So it's observational data, they're not randomized data. It's very difficult to get 10 prime ministers and presidents and tell them that we will randomize you: five of you will get your country to do this, and the other 5 will do that. But we will have a wealth of information to try to understand what really happened. What I want to see happen is not many people lose their lives. I want to see the least number of people lose their lives. And I also want to see the least number of people being destroyed economically, and therefore also losing their lives directly or indirectly because of the consequences.

JK: When do we start pivoting away from this total lockdown? Do you think it's still advisable to be in total lockdown right now? For how this, given the virulence and lethality that we've seen so far, is it - how much longer do you think, from an epidemiological point of view, do we need to wait this out in an economic and social isolation?

DI: As you know, I'm in shelter in place myself now, and I will continue this and I'm okay with this, but I want to get the data to decide whether that should stop. And I think it's inadmissible not to get this data within two or three weeks. It's extremely important, there is too much at stake, and if you tell me, "you're in shelter in place, why don't you break that now?" Well, I have no data. I'm blind and I would be still acting in a blind fashion, and I think that this is not something that I would expect, given our capacity to have good science inform us about the next steps.